The peculiar role of vitamin D in the pathophysiology of cardiovascular and neurodegenerative diseases

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ABSTRACT

Vitamin D is a hormone with both genomic and non-genomic actions. It exerts its activity by binding vitamin D receptor (VDR), which belongs to the superfamily of nuclear receptors and ligand-activated transcription factors. Since VDR has been found in various tissues, it has been estimated that it regulates approximately 3% of the human genome. Several recent studies have shown pleiotropic effects of vitamin D in various processes such as cellular proliferation, differentiation, DNA repair and apoptosis and its involvement in different pathophysiological conditions as inflammation, diabetes mellitus, and anemia. It has been suggested that vitamin D could play an important role in neurodegenerative and cardiovascular disorders. Moderate to strong associations between lower serum vitamin D concentrations and stroke and cardiovascular events have been identified in different analytic approaches, even after controlling for traditional demographic and lifestyle covariates. The mechanisms behind the associations between vitamin D and cerebrovascular and cardiologic profiles have been widely examined both in animal and human studies. Optimization of vitamin D levels in human subjects may improve insulin sensitivity and beta-cell function and lower levels of inflammatory markers. Moreover, it has been demonstrated that altered gene expression of VDR and 1,25D3-membrane-associated rapid response steroid-binding (1,25D3-MARRS) receptor influences the role of vitamin D within neurons and allows them to be more prone to degeneration. This review summarizes the current understanding of the molecular mechanisms underlying vitamin D signaling and the consequences of vitamin D deficiency in neurodegenerative and cardiovascular disorders.

1. Introduction

In the last few decades, vitamin D has become a subject of intensive investigation worldwide, given its pleiotropic effects in various physiological processes as well as the fact that its deficiency is associated with the risk and severity of many diseases such as cancers, cardiovascular diseases, neurocognitive disorders, sarcopenia, osteoarthritis, bacterial and viral infections, inflammatory bowel disease and autoimmune diseases [1–3].

Vitamin D belongs to the group of fat-soluble steroid hormones and exists in two forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), the form on which our work focuses [4,5]. Vitamin D participates in many cellular and molecular mechanisms binding to vitamin D receptor (VDR) [4,6]. In this way, vitamin D regulates the expression of a wide range of genes involved in cellular proliferation, differentiation, DNA repair, apoptosis, and angiogenesis [1,4,6,7].

The primary role of vitamin D is the regulation of calcium homeostasis and thereby the mineralization of bone [8]. However, VDR has been found in various tissues and organs, including cells of the immune system, breast, brain, heart, liver, pancreatic islets, and gastrointestinal

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tract [1]. Therefore, not surprisingly, multiple studies have demonstrated the additional functions of vitamin D, such as immune-modulating effects [9] and its association with glucose homeostasis [4]. Furthermore, several studies have shown an association between vitamin D deficiency and various neurodegenerative pathologies such as multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD) [10].

This review will discuss the current knowledge of vitamin D regarding its immense role in inflammation, diabetes mellitus (DM), cardiac remodeling, anemia and finally, in neurological settings and the consequences following its deficiency or insufficiency.

2. Metabolic activation of vitamin D and its physiology

Vitamin D can be produced endogenously in the skin upon exposure to sunlight, or it could derive from supplements and foods fortified with vitamin D (Fig. 1) [5]. Ultraviolet B radiation (270–300 nm range) induces conversion of 7-dehydrocholesterol to pre-vitamin D3 [2,5,6], which is transported to the liver carried by vitamin D binding protein (VDBP) [5]. In the liver, pre-vitamin D3 undergoes the first of two enzymatic hydroxylations necessary to obtain its biologically active form. More precisely, after the first hydroxylation in the liver at position 25 by CYP2R1 (25-hydroxylase), pre-vitamin D3 converts to 25(OH)D (calcidiol). Finally, in the proximal tubule in the kidney, the second hydroxylation at position one by CYP27B1 (1α-hydroxylase) transforms 25(OH)D into 1,25$(OH)_2$D (calcitriol), the biologically active form [2,11]. Interestingly, it has been demonstrated that several tissues, including lungs, ovaries, intestine, cells of the immune system, pancreatic islets, and the parathyroid gland, possess the CYP27B1 [11,12]. Furthermore, it is worth noting that 1,25$(OH)_2$D synthesis is regulated by serum calcium, phosphorus, magnesium, and parathyroid hormone [4].

The catabolism of 1,25$(OH)_2$D is mediated by CYP24A1, leading to the production of calcitroic acid, which is excreted in bile [13]. CYP24A1 is expressed almost in all cells having VDR and its primary role is to establish negative feedback on the effects and production of 1,25$(OH)_2$D [13].

Vitamin D has both genomic and non-genomic actions [3]. The genomic action of vitamin D is performed by binding to the VDR, which is a member of the nuclear receptor superfamily and ligand-activated transcription factor [3,14]. The VDR is widespread in almost all human tissues, including bones, gastrointestinal tract, kidney, thyroid, parathyroid, and adrenal glands, cells of the immune system such as monocytes, stimulated macrophages, natural killer cells, and activated B and T cells. It is also found in neurons and glial cells, thus playing an immense role in regulating gene expression of approximately 3% of the human genome [10,12,14]. The highest expression of VDR in neurons and glial cells is found in the hippocampus, hypothalamus, thalamus, and substantia nigra [10].

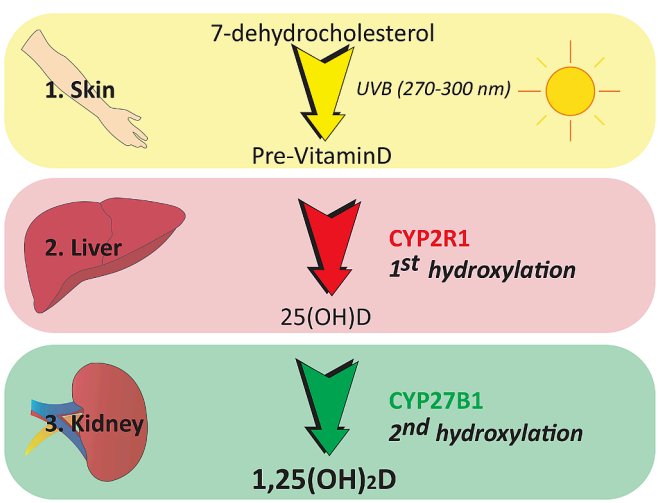

Fig. 1. Metabolism of vitamin D. Ultraviolet B radiation induces the synthesis of vitamin D in the skin, more precisely, it converts 7-dehydrocholesterol to pre-vitamin D. After that step two consecutive enzymatic hydroxylation in liver (2.) and in the kidney (3.) lead to the production of the active form of vitamin D. UVB, ultraviolet B.

VDR consists of three regions: a N-terminal domain with a zinc-finger binding motif to DNA, the C-terminal domain in which 12 alpha-helices create a pocket for the binding of vitamin D, and an unstructured region that tightens together the two functional domains [15]. Upon binding of vitamin D to the VDR, the ligand complex undergoes heterodimerization with other nuclear hormone receptors, particularly with retinoid X receptor [2,11]. The latter complex translocates into the nucleus and binds to specific DNA sequences entitled vitamin D response elements (VDREs) located in promoter regions of the targeted genes [2]. The interaction of VDR with VDRE allows the recruitment of a sizeable coregulatory complex, thus mediating chromatin remodeling [15]. Therefore, this is the mechanism by which vitamin D both upregulates and downregulates the expression of various genes [3].

The non-genomic effects of vitamin D occur when it binds to 1,25D3-membrane-associated rapid response steroid-binding (1,25D3-MARRS) receptor and they are based on the crosstalk with different membranes-mediated signaling pathways [10,16,17]. Indeed, it can rapidly activate various protein kinases such as protein kinase A (PKA), protein kinase C (PKC), proto-oncogene tyrosine-protein kinase Src, and mitogen-activated protein kinases (MAPK) [3,17,18]. By the same token, it has been concluded that these non-genomic activities of vitamin D are not correlated with the regulation of gene transcription, given the fact that mRNA and protein synthesis require more time which is not compatible with the estimated rapid non-genomic effects of vitamin D [19].

Further, one of the most critical roles of vitamin D is the regulation of DNA repair by mechanisms involving BRCA1, p53, and p21waf1 [7]. Vitamin D may act by modulating the activity of intracellular pathways. Inline, it has been shown that it can inhibit cysteine protease cathepsin L, thus stabilizing 53BP-1, a key factor involved in DNA repair.

3. Vitamin D deficiency and supplementation

Given its half-life of two or three weeks, 25(OH)D is the only metabolite evaluated to determine whether individuals suffer from hypovitaminosis D [20]. The proposed optimal range of 25(OH)D is 30–60 ng/ml [1]. Although there is no complete consensus, most experts agree to define vitamin D deficiency as a plasma concentration of 25(OH)D below 20 ng/ml. On the other hand, 25(OH)D levels between 21 and 30 ng/ml and higher than 30 ng/ml are defined respectively as insufficiency and sufficiency of vitamin D [20–23]. There are several causes of hypovitaminosis D, such as alterations in the synthesis pathway, malabsorption, increased catabolism or renal clearance, and hereditary disorders [1]. Worth mentioning, polymorphisms in genes coding for VDBP and nicotinamide adenine dinucleotide synthetase 1 are factors that could influence vitamin D status [24]. It has been reported that 25(OH)D levels between 28 and 40 ng/ml are optimal for ensuring its beneficial effects [25]. The association of lower levels of 25(OH)D with diseases such as type 2 DM (T2DM), autoimmune diseases and neurologic disorders have been extensively evaluated, and the prevalence is chiefly due to seasonal exposure to sunlight [25]. Of note, elderly individuals are frequently diagnosed with vitamin D deficiency mainly due to its impaired absorption and synthesis [26]. Indeed, there is a growing body of evidence to suggest that vitamin D deficiency could contribute to the majority of age-associated pathologies such as cardiovascular diseases, cognitive decline, hypertension, DM, and immune system efficiency, as well as a higher chance of fracture [26].

More specifically, a study, which included an elderly population without cardiovascular disease, previous stroke and dementia, found an

association between vitamin D deficiency and an increased risk of all causes of dementia and AD [27]. Also, it has been observed that low levels of vitamin D are associated with poor outcomes among patients with cardiovascular disease [28] and vitamin D supplementation reduces the risk of cardiovascular events and mortality among individuals with initially low levels of vitamin D and no previous history of myocardial infarction [29]. Furthermore, higher vitamin D levels in serum are associated with a lower risk of T2DM development [30,31]. As well, numerous studies showed that vitamin D supplementation could prevent the development of T2DM [32,33] and could improve glycemic control in patients with already diagnosed T2DM [34]. This evidence broadens our understanding of the importance of vitamin D in preventing the development of these conditions in the general population [25].

Although the consequences of vitamin D deficiency have been thoroughly investigated, it is important to mention the inconsistency regarding studies that aim to show whether vitamin D supplementation could prevent the development of various conditions. Specifically, even though recent studies have shown that vitamin D supplementation can prevent the development of cardiac disease and associated mortality [29,35], many previous studies have failed in this intention. For instance, studies that used monthly high doses of vitamin D showed that supplementation did not prevent cardiovascular disease or cancer among participants enrolled in the study [36,37], nor did it improve mental health [38]. Moreover, a study with daily high doses of vitamin D yielded the same findings [39]. In the same context, studies conducted to assess the beneficial effect of vitamin D supplementation in patients with PD have not shown significant improvements [40], as well as among patients with AD [41]. Possible explanations underlying this inconsistency are multiple. On the one hand, it might be due to the study limitations such as short duration, monthly low doses of vitamin D supplementation or due to high baseline vitamin D concentrations in serum of enrolled participants [42]. On the other hand, studies with high monthly doses of vitamin D failed probably due to the infrequent dosage giving the vitamin D half-life is about two or three weeks. Finally, it is important to mention that many studies evaluated only the baseline concentration of vitamin D in participants without assessing whether patients had exceeded the sufficiency level (30 ng/ml) upon the supplementation. In the same context, it is important to emphasize that the characteristics of patients such as age, body mass index and baseline level of vitamin D should be taken into account when assessing the right dose for supplementation which is different among individuals [43]. Worth mentioning, it has been noted that depending on the vitamin D dose, there is different individual response in terms of gene expression that should be taken into consideration [44]. However, higher doses are associated with genomic alterations several times greater compared to lower doses [44]. Therefore, further studies are needed to clarify this question in detail.

4. General mechanism of immune-modulation through vitamin D

Given its anti-inflammatory role, vitamin D deficiency is suggested as a new risk factor for developing cardiovascular and neurodegenerative diseases [45,46].

In vitro analyses indicate that both endothelial cells (ECs) and immune cells express CYP27B1 and CYP24A1, which means that they can synthesize and degrade 1,25$(OH)_2$D on their own [3,47,48]. In particular, during an immune response, toll-like receptor (TLR) and interferon-γ (INF-γ) mediate the expression of VDR, making cells more susceptible to circulating vitamin D [49]. Moreover, vitamin D mediates its degradation by stimulating the expression of CYP24A1 with negative feedback on the gene expression [47]. Therefore, it has been proposed that vitamin D exerts an autocrine action having a modulatory effect on ECs and immune cells [50]. The effects of vitamin D on these cells are considered crucial for controlling the initiation of systemic immune response via both genomic and non-genomic regulation [51]. Worth mentioning, vitamin D-mediated endothelial regulation is strongly documented. VDR promotes endothelial cell maturation through the Vascular Endothelial Growth Factor (VEGF) [52].

As a part of the complex inflammatory response, genomic regulation following the interaction of vitamin D with VDR results in the down-regulation of the production of inflammatory mediators in ECs. Indeed, vitamin D suppresses the activity of the nuclear factor kappa light chain enhancer of activated B cells (NF-κB), thus reducing the production of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein 1 (MCP-1) (Fig. 2) [50]. In the case of vitamin D deficiency, the increase in the transcription of TNF-α and its receptor causes an increase in oxidative stress and a reduction in nitric oxide (NO) concentration, causing endothelial dysfunction, which is the first step forward in developing the systemic inflammatory state and predisposes to atherosclerosis and myocardial infarction [50]. This finding is also consistent with the recently described down-modulation of vitamin D signaling that occurs in the setting of cellular senescence. It has been demonstrated that vitamin D deficiency is a trigger of cell senescence [7,53]. Significantly, senescent cells accumulate with aging and, in the case of chronic pathologies, are a potent source of inflammatory cytokines that exert detrimental effects on the tissues where they reside [54]. Although VDR binding to VDRE is one of the most known mechanisms of regulating gene expression, the interaction of vitamin D with the 1,25D3-MARRS receptor regulates gene expression through the activation of second messengers as well (non-genomic actions), such as PKC, phosphoinositide 3-kinases (PI3K), phospholipase A2 and MAPK [3].

Further, the non-genomic role of vitamin D in counteracting the inflammatory process consists in maintaining the homeostasis of intracellular calcium through cascades of second messengers [2]. Indeed, intracellular calcium regulates the activity of the endothelial NO synthase (eNOS), which is critical for endothelial function [18]. Specifically, vitamin D supports NO synthesis through the control of PKC by releasing calcium from the endoplasmic reticulum and regulating ion channels on cell membrane via inositol trisphosphate and diacylglycerol [55]. After its release in the cytoplasm, calcium binds to calmodulin that mediates eNOS activation through phosphorylation [55]. Vitamin D can also mediate eNOS phosphorylation via PI3K/protein kinase B (Akt) pathway [55]. Furthermore, the production of cyclic adenosine monophosphate (cAMP) and activation of the PKA has been reported as another mechanism that allows the phosphorylation of eNOS [56]. Given the vitamin D control of cAMP synthesis, it is likely that it can also promote ECs function through this pathway. Furthermore, as pointed out by wide transcriptome analysis in peripheral blood mononuclear cells, vitamin D finely regulates the expression of genes involved in pathways that control cytokines secretion, cell proliferation, differentiation, and function [15,57]. It has been shown to modulate the activation, migration, and function of monocytes [57]. Furthermore, it has been reported that vitamin D promotes T helper 2 lymphocytes (Th2) over T helper 1 lymphocytes (Th1) and thereby increase Th2-mediated anti-inflammatory response [58]. Vitamin D effects extend to the modulation of cytokines production through the regulation of NF-κB translocation to the nucleus [59]. As a result, there is a shift from the production of pro-inflammatory cytokines (i.e., IL-6, IL-12, TNF-α, and INF-γ) to IL-5, IL-10, and IL-13 [2,50].

5. Vitamin D and acute coronary syndrome

According to numerous studies, acute coronary syndrome (ACS) incidence tends to increase during the wintertime [21,60,61]. Worth mentioning, recently published results of an 18-years-old study found no differences in incidence, but compared to other seasons, winter admissions due to myocardial infarction were associated with a higher rate of poor outcome [62]. The reason is multifactorial and one of the causes depend on vitamin D's anti-inflammatory properties. In vitamin D

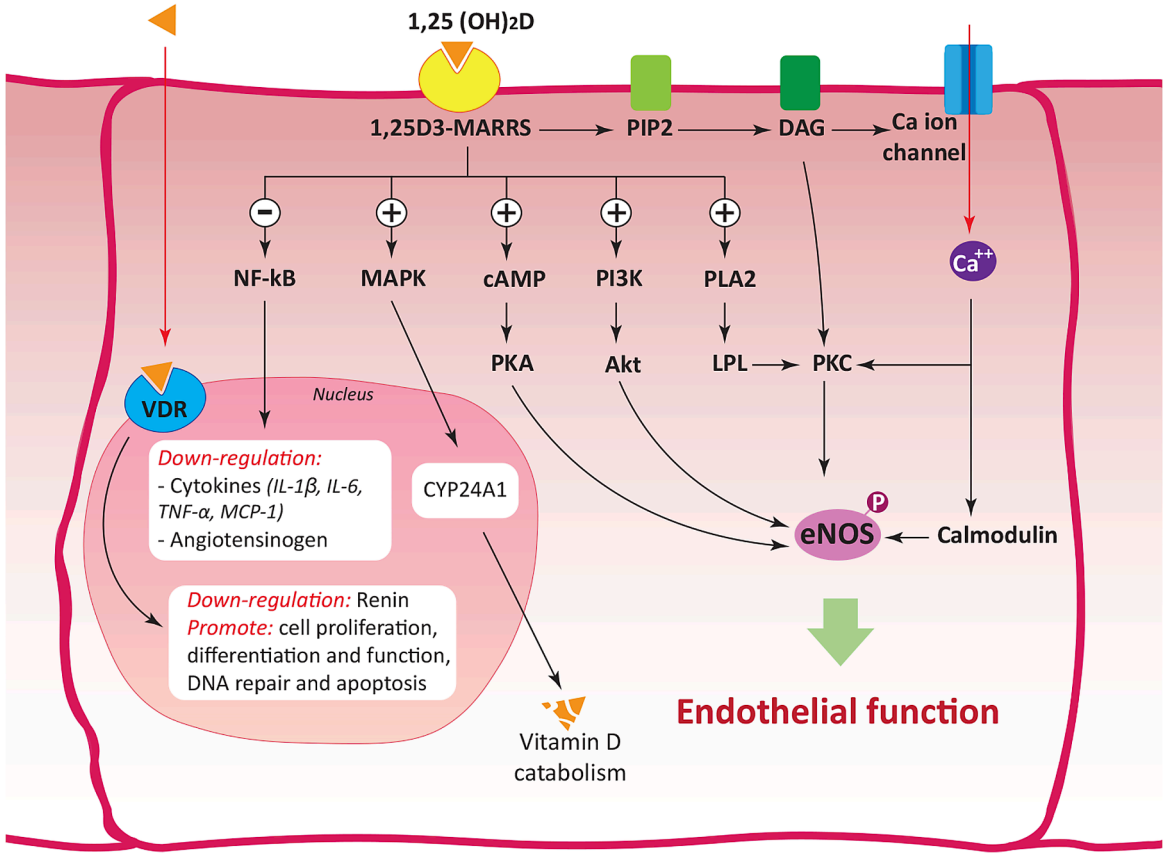

Fig. 2. Genomic and non-genomic action of vitamin D. The genomic effect of vitamin D is mediated by its interaction with VDR. On the other hand, its interaction with 1,25D3-MARRS triggers the non-genomic action of vitamin D through the activation of the second messenger pathways. Vitamin D maintains the homeostasis of intracellular calcium via PIP2 and DAG thus regulating the action of Ca ion channel. Alternatively, vitamin D recruits other second messengers such as cAMP, PI3K and PLA2. All mechanism mentioned above converge on regulating the phosphorylation of eNOS for the proper functionality of endothelial cells. Vitamin D is able to regulate its own catabolism by enhancing the expression of CYP24A1 via MAPK. Moreover, Vitamin D down-regulate the expression of inflammatory mediators (cytokines and angiotensinogen) by inhibiting NF-κB pathway. Akt, protein kinase B; Ca, calcium; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; eNOS, endothelial NO synthase; IL-1β, interleukin 1β; IL-6, interleukin 6; LPL, lipoprotein lipase; MAPK, mitogen-activated protein kinases; 1,25D3-MARRS, membrane-associated rapid response steroid; MCP-1, monocyte chemoattractant protein 1; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; PI3K, phosphoinositide 3-kinases; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLA2, phospholipase A2; TNF-α, tumour necrosis factor alpha; VDR, vitamin D receptor.

deficiency, the prevalence of Th1 causes the increase of INF-γ, which inhibits the production of new collagen, and the activation of macrophages. Inflammatory signaling promotes the production of metalloproteinases (MMPs) such as MMP-1 and MMP-8 [63]. Interestingly, it can also regulate the expression of MMPs and collagen directly through a VDR-mediated mechanism [50]. The result is a higher risk of atherosclerotic plaque rupture due to the reduction of its stability. Moreover, in vitro experiments on ECs suggest that vitamin D can also control platelets, thus affecting thrombotic events after plaque breakdown [50].

Although the formation of atherosclerotic plaque is the leading cause of stenosis of the vascular lumen, other cofactors also participate in the onset of ACS [63]. In particular, given the role of vitamin D in controlling calcium homeostasis, there was great interest in disclosing its role in vascular calcification, which affects vascular rigidity [64]. It has been suggested that vitamin D could regulate calcification modulating VDR-mediated calcium influx or parathormone-related signaling [50]. However, currently available data are still controversial and suggest that the protective effects of vitamin D are likely dose-dependent [50].

Furthermore, experiments on VDR knockout mice indicate elevated activation of the renin-angiotensin-aldosterone system (RAAS). Indeed, elevated blood pressure and cardiac hypertrophy were the most common signs in these animal models [65]. In their study, Li et al. demonstrated that vitamin D inhibits renin gene expression through VDRE on renin gene promoter or by sequestering a fundamental transcription factor [66]. Furthermore, vitamin D hampers the angiotensinogen gene expression by blocking the NF-κB pathway [59]. A large cohort study revealed that circulating levels of both renin and angiotensin II were increased in individuals with vitamin D deficiency than in those with average concentration [65]. These pieces of evidence suggest that vitamin D not only regulates inflammation directly but also via altering the pro-inflammatory activity of angiotensin II.

6. Vitamin D and left ventricular remodeling

Adverse left ventricular (LV) remodeling refers to the molecular, cellular, and interstitial changes that clinically manifest as alterations in ventricular shape and function following cardiac injury, such as ACS. Firstly used in the context of myocardial infarction, the term "remodeling" was then applied also to other forms of myocardial injury and ventricular overload wall stress. Cardiac remodeling can lead to LV systolic dysfunction and the development of heart failure (HF), with a negative impact on prognosis in terms of increased mortality risk and increased hospitalizations for HF. The pathophysiology of pathologic cardiac remodeling includes mechanical alterations (an increase in both preload and afterload) and a broad spectrum of molecular mechanisms and different pathways activation. Specifically, there is a close link between pathologic cardiac remodeling and the activation of several neuroendocrine, paracrine, autocrine, and inflammatory pathways.

Furthermore, the re-expression of fetal genes has been demonstrated as one of the pathophysiological mechanisms underlying adverse cardiac remodeling [67,68].

Several studies have demonstrated an association between vitamin D deficiency and the worst prognosis following myocardial infarction [21,69] and a link between lack of vitamin D and HF progression [70]. As a result, a potential role of vitamin D on LV remodeling has been proposed. Both animal and clinical studies then confirmed this hypothesis. Asselin et al. showed increased cytokine release, oxidative stress, apoptosis, and fibrosis in animals with vitamin D deficiency. In the same animal model, ventricular hypertrophy and lower LV ejection fraction (LVEF) were found at echocardiographic analysis [71]. A recent study on a large cohort of patients with AMI has shown an association between lower vitamin D levels and the risk of developing LV adverse remodeling during follow-up [22]. There is a growing body of evidence that it can play a role in several pathways leading to adverse cardiac remodeling. As mentioned above, vitamin D decreases RAAS activity. Therefore, it is not surprising that among VDR knockout mice, RAAS activity was increased, followed by hypertension, cardiac hypertrophy, and fibrosis as a consequence [66,72].

Another essential mechanism explaining the link between vitamin D and adverse remodeling regards its ability to modulate myocardial extracellular matrix turnover. This turnover is probably mediated by the activation of MMP-9, which can degrade the extracellular matrix, promotes ventricular dilation [73] thus favoring LV adverse remodeling. Increased MMPs activity has been noted among VDR knockout mice. In line with these data, Foroughinia et al. showed that serum MMP-9 levels were inversely correlated with vitamin D [70,74,75]. Furthermore, as previously explained in this paper, vitamin D deficiency is strongly associated with inflammation, which has also been demonstrated to be a key determinant of adverse cardiac remodeling [67,68].

Given these pieces of evidence on the role of vitamin D on LV remodeling, it has been suggested that supplementation of vitamin D may improve the prognosis of patients with HF, and several studies have been conducted to evaluate the effect of vitamin D supplementation. Zhang et al. demonstrated that application of vitamin D reduced pressure overload-induced contractile dysfunction, cardiac hypertrophy, fibrosis, and inflammation in mice [76]. In the VINDICATE study, the effects of vitamin D supplementation in patients affected by HF due to ischemic and non-ischemic LV systolic dysfunction and vitamin D deficiency, significantly improved LVEF volumetric parameters compared to the placebo group [77]. A meta-analysis by Zhao et al. demonstrated decreased left ventricular end-diastolic dimension and increased LVEF in patients treated with vitamin D compared to the control group [70]. At the same time, other studies failed to demonstrate a clinical benefit of vitamin D supplementation, primarily because of design limitations, such as short duration and insufficient statistical power, and various other reasons such as too low doses of vitamin D or infrequent dosage [36,42,78].

Another issue is that many studies suggested J and U-shaped relation between vitamin D levels and prognosis; in particular, it was shown that patients with intermediate levels of vitamin D had a better outcome than those with both low and higher levels of vitamin D [79–81]. U.S. Nationally Representative NHANES [79] and Copenhagen vitamin D study (CopD-study) [80] suggested a reverse J-shaped relationship between vitamin D levels and all-cause and cardiovascular mortality, pointed out that low as well as high levels of vitamin D lead to the unfavorable outcome. Our group, in a study involving patients with AMI, showed that a higher mortality rate was associated with extreme levels of vitamin D such as <10 ng/ml and >30 ng/ml compared with those with intermediate levels, suggesting the U-shape relationship between vitamin D concentration and long-term mortality [82]. Furthermore, even after adjusting for differences in baseline characteristics, extreme levels of vitamin D remained independent predictors of long-term mortality [82]. Although the association between low vitamin D levels and cardiovascular mortality has been thoroughly investigated in clinical studies, indicating the link between vitamin D deficiency and increased pro-inflammatory cytokines, rise in RAAS activity and endothelial dysfunction, factors already recognized as promoters of LV remodeling after myocardial infarction, the molecular pathways involved in the association of higher vitamin D levels and adverse events are still lacking. One of the proposed explanations is extensive calcium phosphate deposits in the arteries and vascular calcification [82]. Noteworthy, several studies conducted to investigate the J- and U-shape relationships between extreme doses of vitamin D and their negative prognostic power advocate the inaccuracy of these data and point to possible explanations of the same. Apart from design limitations such as small cohort, non-appropriate adjustments, the onset of vitamin D supplementation immediately prior to enrollment in cohorts is an important risk factor for U-shaped relationships between vitamin D and unfavorable outcome [81]. Grant et al., tried to explain the possible reasons for this confusing issue, pointing out that U-shape relationship could be result of a certain lifestyle or the appearance of a disease due to the vitamin D deficiency masked by supplementation that started too late to affect the progression of undergoing disease [83]. In support of these claims, a 7-year-old study by McCullough et al. pointed out that several years of daily vitamin D supplementation in the range of 5000 IU/d to 60,000 IU/d were safe for participants indicating that high doses of vitamin D can be tolerated [84]. This imposes the hypothesis that in only cases of severe overdose, vitamin D supplementation can lead to disastrous consequences. For this reason, further trials are needed to evaluate optimal vitamin dosage, appropriate dosing frequency, and the effects of vitamin D supplementation in the long term [76].

7. Vitamin D and diabetes mellitus

Several studies have demonstrated that vitamin D deficiency is correlated with reduced insulin secretion, and it has been noted that it could affect glucose intolerance [12,85]. Norman et al. showed reduced insulin secretion in the pancreas islets in rats with vitamin D deficiency and that it can be restored after vitamin D supplementation [86]. In another study, Bland et al. demonstrated that pancreatic islets could locally convert 1,25$(OH)_2$D from circulating 25(OH)D, proving the 1α-hydroxylase activity in the pancreas and rapid response to the treatment with vitamin D [87].

Accumulating evidence has proven that vitamin D has both genomic and non-genomic actions in the pancreas. Even though a high concentration of VDR has been found in pancreatic tissue [12], its exact role both in glucose homeostasis and in maintaining the maturity of beta cells remains unclear and further investigation are needed [88]. Vitamin D stimulates insulin synthesis and regulates insulin secretion by increasing calcium concentration (due to non-selective voltage-dependent calcium channels) thereby, in cases of vitamin D deficiency, insulin secretion is reduced [12,88].

A high glucose concentration in the blood of patients with T2DM induces both local and systemic inflammation due to oxidative stress [89–92]. Advanced glycation end products are recognized as a risk factor for type 1 DM, beta-cell dysfunction, and insulin resistance [89]. In the same context, ROS species trigger inflammatory signaling pathways by activating many transcription factors resulting in the synthesis of pro-inflammatory cytokines, such as IL-6 and TNF-α [93]. ROS-activated signaling pathways involving NF-κB and PKC could interfere with the insulin signaling pathways leading to insulin resistance [91]. In addition, high glucose levels as well stimulate RAAS, and therefore, angiotensin II activated the NF-κB signaling pathway promoting the expression of pro-inflammatory cytokines.

Vitamin D deficiency is common among patients with DM, and lower levels of vitamin D are associated with disease complications [23]. As mentioned in previous chapters, it has a significant anti-inflammatory role, and vitamin D deficiency is related to an altered inflammatory state [50]. Vitamin D suppresses the NF-κB pathway thus reducing the angiotensin II-induced expression of pro-inflammatory cytokines [23].

Last, a crucial player linking insulin resistance, autophagy suppression, and cellular senescence with inflammation is the mTOR pathway [94]. Intriguingly, it has been reported that vitamin D can suppress mTOR signaling by promoting the expression of DNA damage-inducible transcript 4 (DDIT4) [95].

In conclusion, considering all factors mentioned above, several studies have already suggested that optimizing vitamin D levels could improve insulin sensitivity and beta-cell function and lower levels of inflammatory markers [96]. This approach is beneficial on many levels since vitamin D deficiency combined with DM contributes to the progression of various cardiovascular complications [23]. Indeed, the persistently high glucose concentration in the blood of patients suffering from DM causes vascular damage, which over time affects the heart [97]. Several studies have been conducted to estimate the relationship between vitamin D levels and the severity of coronary artery atherosclerosis among patients diagnosed with DM. Since DM is recognized as a risk factor for coronary artery disease (CAD), the correlation between vitamin D and DM could explain the link between vitamin D deficiency and CAD, which is usually related to poor outcomes. Moreover, Gundam et al. showed that vitamin D deficiency correlated with more severe forms of ACS, and patients with T2DM had more lesions in the coronary angiography than patients without DM [98]. In another study involving 337 cardiac patients with T2DM undergoing coronarography, lower levels of vitamin D were found in patients with significant lesions in coronary arteries and those hospitalized due to the ACS, and individuals with a previous history of myocardial infarction [96]. Recently, our group published a study involving a large population of patients who survived an AMI, showing for the first time that DM and low vitamin D levels have similar negative prognostic values relative to patient outcome. Specifically, our results demonstrated that DM and vitamin D deficiency were associated with an unfavorable outcome either when considered individually or together [23].

8. Vitamin D and anemia: an emerging link

Several findings have pointed out an emerging association between anemia and low vitamin D levels in a healthy and diseased populations. Despite possible confounders due to the fact that diseases that cause anemia and vitamin D deficiency often coexist, it has been proposed that vitamin D may play a role in iron metabolisms and erythropoiesis [99]. It seems that vitamin D deficiency could lead to anemia secondary to inflammatory states (anemia of inflammation). Perlstein et al. examined the association between vitamin D levels and anemia in more than 5000 subjects. Besides finding a strong correlation between vitamin D deficiency and the prevalence of anemia, the authors indicated that vitamin D deficiency was associated with anemia of inflammation compared with unexplained anemia [100]. The pathophysiological explanation of the vitamin D and anemia association may lay in the ability of vitamin D to downregulate several pro-inflammatory cytokines and the acute phase reactant hepcidin, thus increasing iron availability. Indeed, hepcidin is responsible for iron-limited erythropoiesis which characterizes both acute and chronic inflammatory states. Hepcidin binds to the cellular iron exporter, ferroportin, and promotes its degradation, thus reducing intestinal iron absorption and blocking the iron release from cells such as macrophage, favoring iron deposits. These alterations in the iron metabolisms may lead to a depressed erythropoiesis due to insufficient iron availability [99,100].

While elevated hepcidin levels have been demonstrated in patients with anemia of inflammation, the mechanisms through which vitamin D levels influence hepcidin expression are not clear yet [100]. Being hepcidin induced by IL-6 [101], it has been suggested that vitamin D may influence hepcidin expression by acting as a suppressor of IL-6. This finding is supported by a study conducted by Zughaier et al. showing a dose-dependent decrease in IL-6 levels in human monocyte cells in the presence of increased vitamin D concentrations [102]. Direct action of vitamin D on hepcidin gene expression may also be possible, since vitamin D response elements in the promoter region of the hepcidin antimicrobial peptide gene have been described [103]. Based on these data, vitamin D deficiency may contribute to anemia, in particular anemia of inflammation, by the loss of vitamin D anti-inflammatory effect on IL-6 and by the reduction of vitamin D mediated hepcidin expression [99]. Alternatively, it cannot be excluded that vitamin D deficiency and anemia are merely the results of the same inflammatory pathways [100].

Vitamin D deficiency has been proposed to contribute to a decreased erythropoiesis independently of the hepcidin-mediated iron deficiency. In fact, on one side inflammatory cytokines, not counteracted by vitamin D anti-inflammatory effects, may inhibit the production of erythropoietin and limit the differentiation and proliferation of erythroid progenitor cells. On the other hand, it appears to play an essential role in erythropoiesis because it is involved in increasing burst-forming unit-erythroid proliferation since it has a synergistic effect with erythropoietin in further erythroid progenitor cell proliferation [99].

The role of vitamin D levels on iron metabolisms and erythropoiesis is further supported by some clinical trials investigating the effects of vitamin D supplementation. A recent meta-analysis, which included 14 randomized controlled trials, found that vitamin D supplementation positively affected transferrin saturation and serum iron, although no significant improvement in hemoglobin or ferritin levels was observed [104].

It is known that iron deficiency could be detrimental in patients with cardiovascular disease, such as CAD, HF, pulmonary arterial hypertension (PAH) and patients candidate to cardiac surgery. Furthermore, iron deficiency is prevalent among these patients, affecting around one-third of patients with HF and 50% of those with PAH [105]. While little data are available for the role of iron deficiency and anemia in CAD and PHA, more is known about their impact in patients with HF. Data suggests that the prevalence of iron deficiency is elevated in patients with CAD and appears to increase mortality, especially in patients with other comorbidities such as DM. However, there is no clear evidence on the possible effects of iron supplementation in these patients [105]. The prevalence of iron deficiency was found to be high in patients with PAH as well. PAH patients with iron deficiency were found to have higher values of pulmonary artery pressure and N-terminal prohormone BNP (NT-proBNP), as well as a reduced cardiac index in comparison with those with normal iron levels [106]. Another study demonstrated that among patients with PAH those with iron deficiency had lower levels of serum ferritin and increased hepcidin and were at increased risk of mortality [107]. A pilot study to investigate the effect of intravenous ferric carboxymaltose in a small group of PAH patients with iron deficiency demonstrated improvement in six-minute walking test distance and patients' quality of life [107,108].

In patients with HF, anemia is a common condition, its prevalence increasing with the severity of the disease, and it is associated with higher mortality risk in several studies and meta-analyses, even after adjustment for other potential confounders. Moreover, anemia in patients with HF has been associated with poor quality of life, reduced exercise capacity, increased hospitalization and higher natriuretic peptides levels. While most studies found hemoglobin values to be inversely but linearly related to adverse outcomes, there is evidence that suggests that the highest hemoglobin levels could be associated with adverse prognosis, thus suggesting a U shape relationship [106,107].

Anemia and iron deficiency, although usually connected, could also exist independently and their pathophysiology in the context of HF is not yet completely understood [109]. Often, instead of one etiology, anemia and iron deficiency in the setting of HF are more likely to be the result of multiple contributing factors, first of all, the systemic inflammatory state, which characterizes chronic HF. Other essential elements could be renal dysfunction, drugs used, abnormal steroid metabolism and finally vitamin D deficiency [108–110].

The idea of improving anemia state using a combination of erythropoietin and iron sucrose for ameliorating cardiovascular outcomes in

patients with HF proved successful, leading to improvements in NYHA class, hemoglobin levels and LVEF in a small cohort of patients. These results were further confirmed by several larger randomized controlled trials [105,110]. Sever studies have then assessed the impact of the management of intravenous iron in patients with chronic HF. The results demonstrated a clear benefit of this treatment in patients with chronic HF and iron deficiency, both with and without anemia. This treatment has already been listed in ESC guidelines [111].

From all evidence presented above, we can therefore hypothesize that iron imbalance and anemia could be one of the potential pathways through which vitamin D deficiency could hurt the prognosis of several cardiovascular diseases.

9. Vitamin D and neurologic disease

Accumulating evidence shows that vitamin D is essential for proper brain development, maturation, functions, and neural network development [10]. Vitamin D deficiency has emerged to be related to various neurological conditions such as MS, PD and AD [10,112], however, the majority of clinical studies failed to prove the beneficial effect of vitamin D supplementation among patients with PD and AD [40,41].

The most critical and recognized implication of vitamin D is its active participation in the modulation of neuroinflammation, which is associated with neurodegenerative diseases [112,113]. Many examples should be cited; the most popular of these is that cells of the innate and the adaptive immune system express the VDR, and immune cells present the rate-limiting enzyme, which promotes the vitamin D synthesis (CYP27B1) [114–116]. Generally, there is solid evidence that vitamin D is involved in the regulation of the inflammatory response, modulating the induction and differentiation of the major histocompatibility complex (MHC) class II expression, CD40, CD80, CD86, and IL-10 and 12, leading to reduced T cell stimulatory capacity [117–121], and promoting the transition from a pro-inflammatory autoimmune response to a "tolerogenic" immune response [121,122]. These aspects strongly related vitamin D to the experimental autoimmune encephalomyelitis (EAE) and its clinical counterpart, MS. Therefore, vitamin D regulates the mechanisms of tolerogenic regulation. Thus, it helps the innate switch between active-damage-related inflammation processes towards the active-repair-related inflammation system in MS [10,123]. Many pieces of evidence stated a powerful help exerted by vitamin D in the microglial activation in MS, promoting the clearance of myelin debris [10,124,125] and up-regulating the expression of the oligodendrocyte precursor cells (OPC) [126–132]. A critical study, which demonstrated a strong relationship between lower levels of vitamin D, estrogen stimuli and signs of EAE, showed that whenever female mice were properly supplemented by vitamin D, the histopathology of the immune response was better than that observed in ovariectomized females and intact or castrated males [133]. Another similar study advocates a strong synergy between estradiol expression and vitamin D through the VDR-mediated enhancement of estradiol synthesis and the estradiol-mediated enhancement of VDR expression in central nervous system inflammation [134], suggesting the possibility that vitamin D-mediated protection in EAE is female-specific. In addition, several genome-wide association studies have found an association between a genetic predisposition to lower levels of vitamin D and an increased rate of MS progression [135–137], verified by a retrospective study of pediatric-onset MS, in which an increase of 10 ng/ml of vitamin D was associated with a 34% decrease in the relapse risk [138].

The inflammatory modulation seems to have an influential role in the ischemic models of cerebrovascular disease. Therefore, vitamin D is being actively studied in this context with partial but fundamental experimental conditions, simulating vascular disease in neuronal cell cultures. As mentioned above, vitamin D plays an important role in the microglial activation and regulation, and in the reduction of the activation of MAPK and NF-κB pathways promoting an anti-inflammatory state [10,139]. Also, vitamin D inhibits the expression of MMP-2 and MMP-9 [140] and reduces the activity of the platelet-derived growth factor, which in turn increases thrombomodulin [141]. Vitamin D deficit is therefore associated with the promotion of atherogenic pro-inflammatory cytokines that destabilize the plaques and promoting thrombotic plaques expansions and altering endothelial response [142]. Furthermore, one of the main mechanisms is the inverse correlation between low vitamin D levels and higher levels of high sensitivity C-reactive protein (hsCRP) [143]. CRP acts on endothelium, promoting the up-regulation of tissue factors, up-regulating plasminogen activator inhibitor expression and inducing the production of pro-inflammatory cytokines through NF-κB activation [144–146]. Worth mentioning, vitamin D might act as a potent regulator of autonomous control of small vessels throughout the body (bones, parenchyma, and brain) [147–149]. Indeed, through calcium control, vitamin D indirectly regulates, at least, brain small profound arteries, helping in the vessel regulation of constant blood supply inside the brain and possibly, mediating the correct function of the neurovascular coupling [10,150–153]. Even in clinical practice, laboratory findings have documented, albeit very distant, unquestionable conditions for the universal acceptance of vitamin D as a clinically modified risk factor for vascular diseases. At present, vitamin D has some documented proof of being a risk factor for ischemic stroke prognosis [154–157], after corrections for age, race, sex, systolic blood pressure, body mass index, DM, smoking, and atrial fibrillation [158–160].

Given the fact that oxidative stress is implicated in neurodegenerative diseases, it is important to emphasize the antioxidant role of vitamin D [161,162]. It is known that adequate vitamin D supplementation protects ECs from damage caused by advanced glycation products [163]. In a study by Velimirovic et al., vitamin D supplementation prior to induced ischemia/reperfusion reduced oxidative stress and Nicotinamide Adenine Dinucleotide Phosphate Hydrogen oxidase (PHOX) 2 and MMP-9 production in the brains of experimental animal models [161]. Also, it has been recently accepted that small vessel disease-related dementia is also determined by increased activity of PHOX [164,165]. As a significant superoxide-producing enzyme complex, phagocytic PHOX is essential for host defense, and it has been found even in astroglia and neurons [166]. An emerging body of evidence pointed out the crucial role of overactivated PHOX in neuroinflammation and neurodegeneration and that suppression of PHOX activity is associated with reduced neuronal damage in neurodegenerative diseases models [166]. PHOX-derived ROS act as potent vasodilators through H_2O_2 production, or by reducing NO bioavailability, as well as via regulation of various signaling molecules and second messengers [167].

It is extremely important to mention the neuroprotective role of vitamin D due to the regulation of calcium homeostasis in brain neurons. Cultured hippocampal cells treated with high doses of vitamin D were protected from age-related excitotoxicity, promoting a strong down-regulation of L-type voltage-sensitive calcium channels [168,169], which surge is usually expected to occur in aging hippocampal cells and in damaged cells [170,171]. Vitamin D regulates the expression of 74 genes and 36 proteins, connected with the correct development of the cytoskeleton and it mediates the post-transcriptional controls of L-type voltage-sensitive calcium channels [172,173]. The L-type voltage-gated calcium channels (L-VGCCs), a significant route of calcium influx, are a part of the high-voltage activated family [174]. They were named "L" for their long-lasting inward currents during the depolarization process, as studied in neurons and cardiac myocytes, and they are sensitive to 1,4-dihydropyridines [174]. Mediating the down-regulation of mRNA expression for different subunits of L-type voltage-sensitive calcium channels [175], vitamin D regulates calcium influx currents and their complex homeostatic related activities, and therefore, most importantly, the apoptotic induction and the neuronal death [169]. Indeed, VDR knock-out mice have a more significant induction of apoptosis and precocious signs of neuronal death [171,176] and show altered expression of different neurotrophins [177]. In addition, it has been demonstrated that polymorphic altered expression of VDR (such as Bsm-

I and Taq-I variants of VDR polymorphism), have altered neurons' resistance to calcium, being more prone to neurodegeneration [10]. Furthermore, VDR polymorphisms have been thoroughly studied in AD [178,179]. On these results, the studies reported that various VDR polymorphism induces an inflammatory context, predisposing to altered macrophages demolition of insoluble amyloid deposits, inhibiting the inducible NO synthase, and therefore promoting the hyperphosphorylation of tau protein (with the consequent tau aggregation, microtubule dissociation and inducing neural starvation) [10,180,181]. In addition, Kasatkina et al. recently demonstrated that vitamin D deficiency increases the risk of various neurological disorders due to the promotion of a pro-inflammatory state and a presynaptic increase in calcium [182]. The group showed that the increase of glutamate level and unstimulated GABA release were connected with the increased ROS and higher calcium influx, thereby increasing excitability in animal models with vitamin D deficiency. Most importantly, vitamin D supplementation was able to recover the shift of unstimulated GABA release due to vitamin D deficiency, whereas the glutamate levels were only partially recovered, pointing out once again the neuroprotective role of vitamin D [182].

Further, since glutamate exerts its neurotransmission activity through *N*-methyl-D-aspartate receptor (NMDAR) and since long-terms increase of extracellular glutamate causes an excessive NMDAR activity and excitotoxicity which is directly linked to neurological disorders such as schizophrenia, AD, MS, vitamin D loss implies an alteration of the NMDAR's function due to the increase of glutamate as explained above [183]. Interestingly, as the brain ages, the function of NMDAR is reduced, leading to widespread neurodegeneration which is quite common, per se, in AD amyloidopathy and neuroinflammation conditions. A severe and persistent NMDAR hypofunction can as well lead to widespread neurodegeneration with accompanying mental symptoms and further cognitive deterioration as well [184].

Finally, but not negligible, there is consolidated evidence of the non–genomic roles of vitamin D in PD due, as in other neurodegenerative diseases, to a substantial interference with L-type voltage-sensitive calcium channels and a pro-inflammatory induction state [185–188]. Nevertheless, cytochrome (CYP) P450, particularly CYP2D6, expressed in neurons and the gut has a polymorphic expression in PD [188]. CYP2D6 works as a 25-hydroxylase and its deficiency is involved in a severe hypovitaminosis-D state. The genes codifying for CYP2D6 are located on chromosome 22 [189], where many genes correlated to PD disease are located as well (chromosome 22q11.2 deletion syndrome and early-onset PD) [190–192]. In addition, it seems that vitamin D inhibits the activity of Poly (ADP-Ribose) Polymerase-1 (PARP1) [193], a stress protein, which is over-expressed in the substantia nigra of PD patients [194]. Specifically, PARP1 is important for the maintenance of genome integrity, protecting the cell from oxidative stress and preventing DNA damage. However, excessive PARP1 activation promotes neuronal death [194]. That could further explain additional beneficial mechanisms of vitamin D supplementation among patients with PD even though there is an inconsistency regarding studies with the aim to demonstrate the valuable effects of vitamin D [40,195].

10. Conclusions

Our review summarizes current knowledge regarding vitamin D, its multiple beneficial roles in various tissues and organs, with a special focus on vitamin D deficiency and its consequences on cardiovascular and neurodegenerative disorders. We thoroughly review the important immune-modulating effects of vitamin D and its association with glucose homeostasis, immense anti-oxidative role, different metabolic regulation processes, and metal deposit regulatory effects both in cardio and neuro settings. Also, we discuss the relationship between vitamin D and LV remodeling, anemia and DM, and the conditions in which vitamin D deficiency has been linked to the worst clinical picture and in which several studies demonstrated the condition amelioration due to the vitamin D supplementation. All these aspects lead us to expand to other future roles of vitamin D in many different, unknown biochemical and genetic functions, which can support the emergent idea of a polyhedron, an indispensable hormone, and not just a vitamin whose amount helps our bones and nothing more. So far, there is an inconsistency indicated by studies related to vitamin D supplementation, which has failed to demonstrate a reduction in the risk of developing various neurodegenerative diseases such as MS, PD and AD, as well as cardiovascular diseases and concomitant mortality, probably due to poor study set up. However, further studies are needed to confirm the beneficial effect of vitamin D supplementation. Also, it is of the utmost importance to properly apply therapeutic drug management in vitamin D supplementation settings, individually adjusting the dose taking into account patient characteristics such as age, body mass index and baseline vitamin D levels and monitoring the concentration of vitamin D during supplementation for better results.

Abbreviations

ACS	acute coronary syndrome
AD	Alzheimer's disease
Akt	protein kinase B
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CYP	cytochrome
DDIT4	DNA damage-inducible transcript 4
DM	diabetes mellitus
T2DM	diabetes mellitus type 2
EAE	experimental autoimmune encephalomyelitis
ECs	endothelial cells
eNOS	endothelial NO synthase
HF	heart failure
hsCRP	high sensitivity C-reactive protein
IL	interleukin
INF-γ	interferon-γ
LV	left ventricular
LVEF	left ventricular ejection fraction
L-VGCCs	L-type voltage-gated calcium channels
MAPK	mitogen-activated protein kinases
1,25D3-MARRS	1,25D3-membrane-associated rapid response steroid
MCP-1	monocyte chemoattractant protein 1
MHC	major histocompatibility complex
MMPs	metalloproteinases
MS	multiple sclerosis
NMDAR	*N*-methyl-D-aspartate receptor
NT-proBNP	N-terminal pro hormone BNP
NO	nitric oxide
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
OPC	oligodendrocyte precursor cells
PAH	pulmonary arterial hypertension
PARP1	Poly (ADP-Ribose) Polymerase-1
PD	Parkinson's disease
PHOX	NADPH oxidase
PI3K	phosphoinositide 3-kinases
PKA	protein kinase A
PKC	protein kinase C
RAAS	renin-angiotensin-aldosterone system
Th1	T helper 1 lymphocytes
Th2	T helper 2 lymphocytes
TLR	Toll like receptor
TNF-α	tumour necrosis factor alpha
VDBP	vitamin D binding protein
VDR	vitamin D receptor
VDREs	vitamin D response elements
VEGF	vasoactive endothelium-derived growth factor

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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